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EXHIBIT II

Facial Skeletal Augmentation Using Hydroxyapatite Cement

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resorption

This study investigates the use of a new calcium phosphate cement, which sets to solid, microporous hydroxyapatite, for facial bone augmentation. In six dogs, the supraorbital ridges were augmented bilaterally with this hydroxyapatite cement. On one side, the hydroxyapatite cement was placed directly onto the bone within a subperiosteal pocket. On the opposite side, the cement was contained within a collagen membrane tubule and then inserted into a subperiosteal pocket. The use of collagen tubules facilitated easy, precise placement of the cement. All implants maintained their original augmented height throughout the duration of the study. They were well tolerated without extrusion or migration, and there was no significant sustained inflammatory response. Histologic studies, performed at 3, 6, and 9 months revealed that when the cement was placed directly onto bone, progressive replacement of the implant by bone (osseointegration of the hydroxyapatite with the underlying bone) without a loss of volume was observed. In contrast, when the cement-collagen tubule combination was inserted, primarily a fibrous union was noted. Despite such fibrous union, the hydroxyapatite-collagen implant solidly bonded to the underlying bone, and no implant resorption was observed. Hydroxyapatite cement can be used successfully for the experimental augmentation of the craniofacial skeleton and may be applicable for such uses in humans.

(*Arch Otolaryngol Head Neck Surg.* 1993;119:185-190)

A wide variety of implant materials are currently being used for facial skeletal augmentation and reconstruction. The most commonly used materials are bone, cartilage, and polymeric alloplasts. Each of these implants has significant limitations. Autogenous bone grafts have the disadvantages of donor site morbidity, limited quantity, variable resorption, and unpredictable remodeling of the graft.[1-4] Allogenic bone grafts can demonstrate resorption rates as high as 82%.[5-8] In an attempt to find an improved implant material, alloplasts such as silicone (Silastic, Dow Corning Wright, Arlington, Tenn) polyamide mesh (Supramed, Jackson Inc, Alexandria, Va), porous polytef (Proplast, Novamed Inc, Houston, Tex), high-density porous polyethylene (Medpor, Interpore International, Irvine, Calif) and methylmethacrylate have been developed. These alloplasts are also less than ideal. Silastic, Supramid, Proplast, and Medpor become encapsulated with scar tissue and do not integrate with host tissue, resulting in implant instability.[9-15] Implant movement at the implant–host tissue interface stimulates an inflammatory response, contributing to implant infection and extrusion.[15] Methylmethacrylate implants are also associated with local tissue necrosis and foreign body giant cell reaction, elicited by the exothermic polymerization phase at the time of implantation.[16,17]

Currently, there is no ideal implant material for facial skeletal augmentation in clinical use. Such an ideal implant material should have several key characteristics: it should (1) have excellent tissue compatibility; (2) be available in unlimited quantities; (3) be easily contoured; (4) retain stable shape over time; and (5) become ingrown or replaced by living tissue. One compound with such properties is hydroxyapatite. The majority of the human skeleton is composed of hydroxyapatite, and it is therefore considered a chemically "natural" compound by the body. Inflammatory responses or toxic reactions in the surrounding host tissue have not been demonstrated with hydroxyapatite implants.[18,19] Perhaps the most important characteristic of hydroxyapatite is its osteoconductivity. It induces the growth of host bone onto the implant, ultimately encasing the implant with host bone.[18-20] This promotes implant stability and maintains implant volume.

Clinical application of hydroxyapatite began in the mid-1970s, primarily within the fields of oromaxillofacial surgery and dentistry for alveolar ridge augmentation and repair of dental defects.[21-25] The hydroxyapatite preparations used clinically have been in "ceramic" form. Ceramic hydroxyapatite is commercially available in dense and porous forms, each manufactured as blocks or granules. Of the various ceramic hydroxyapatite compounds that have been used, the porous form most consistently promotes osseointegration, resulting in the formation of a strong bond between the hydroxyapatite implant and the adja-

Accepted for publication July 10, 1992.

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cent bone. Experiments in laboratory animals have shown that osteoid tissue grows into implanted porous ceramic hydroxyapatite blocks, sometimes extending beyond the height of the original bone surface.[19,20] Though blocks of ceramic hydroxyapatite can be substituted in specific applications for bone grafts, their use has been limited by the need to fabricate this material as a hard implant, which is fragile and difficult to sculpt to facial skeletal defects. The granular form of hydroxyapatite also has limitations in clinical application owing to a lack of structural stability and difficulty in containing the granules within the area requiring reconstruction.

"Nonceramic" hydroxyapatite (hydroxyapatite cement) was developed to overcome these significant limitations of ceramic hydroxyapatite. Unlike ceramic hydroxyapatite, which is preformed, the nonceramic hydroxyapatite forms a cement when mixed with water. This cement primarily consists of tetracalcium phosphate and dicalcium phosphate anhydrous, which react in an aqueous environment to form hydroxyapatite at a physiologic pH and temperature (Fig 1).[26,27] As the only product of this reaction is hydroxyapatite, the resultant implant is highly compatible with bone and soft tissues. This cement has been successfully used for frontal sinus obliteration and cranioplasty in the cat model. Results of experiments by Chow and coworkers and Costantino and coworkers[28-31] showed that this sparingly soluble hydroxyapatite implant resorbed with time but was replaced with living bone in an approximate 1:1 ratio and resulted in no significant loss of implant volume. This cement has just begun to undergo clinical evaluation in humans for use in calvarial reconstruction. The purpose of this study was to evaluate the feasibility and efficacy of using this nonceramic hydroxyapatite cement for augmentation of the non–stress-bearing craniofacial skeleton.

MATERIALS AND METHODS

Experimental Design

Six healthy adult mixed-breed dogs weighing between 20 and 23 kg were chosen for the study. The protocol and guidelines for this study were approved by the Institutional Animal Care and Use Review Committee of Northwestern University Medical School, Chicago, Ill. The preoperative and postoperative care of these dogs was overseen by the university veterinarians to ensure proper and humane treatment. The hydroxyapatite cement for the study was manufactured and supplied by the American Dental Association Health Foundation. Gamma radiation is the only acceptable method of sterilization for this substance. As this method was not available, the hydroxyapatite cement was not sterilized before implantation. The hydroxyapatite cement was mixed with saline to create a thick paste. The paste was used to augment the supraorbital ridges bilaterally. On one side, the cement was inserted into a previously created subperiosteal pocket. On the other side, the cement was contained within a collagen membrane tube and then inserted into a similar subperiosteal pocket. The hypothesis was that cement contained within a collagen membrane tubule would demonstrate easier handling during surgery as compared with the uncontained "free" cement. The concept of using collagen tubules to contain the hydroxyapatite cement was based on favorable results from human and animal studies using collagen tubes to contain ceramic hydroxyapatite particles when implanted onto the alveolar ridge.[32,33]

Two dogs were killed at 3 months (group 1), two at 6 months (group 2), and two at 9 months (group 3). Histologic examinations and histomorphometric studies of the implants were performed to assess the long-term outcome of the implants.

$$Ca_4(PO_4)_2O + CaHPO_4 \xrightarrow{H_2O} Ca_5(PO_4)_3OH$$

Fig 1.—*Reaction of tetracalcium phosphate and dibasic calcium phosphate at physiologic pH in the presence of water to produce hydroxyapatite.*

Operative Technique

Surgery was performed under general anesthesia by administering halothane endotracheally after induction with intravenous 4% pentobarbital sodium (0.5 mL/kg). A midline 5-cm vertical incision was made over the forehead, extending from the nasion to the skull. A 1-cm periosteal incision was made over each supraorbital rim, and the periosteum was elevated to create subperiosteal pockets (Fig 2, left). Immediately before use, the hydroxyapatite cement was mixed with sterile water (0.3 mL/g of cement) to obtain a thick paste. Half of the paste was inserted into an 8-mm-diameter collagen membrane tubule (COLLA-TEC Inc, Plainsmore, NJ). The membrane has a pore size of less than 400 nm. The hydroxyapatite-collagen tubule was inserted into the left subperiosteal pocket (Fig 2, right). On the right side, the hydroxyapatite paste was placed directly onto bone using a small periosteal elevator, thereby filling the subperiosteal pocket (Fig 2, right). The periosteum and the skin incisions were closed in two layers with absorbable sutures. The height of the implant was measured on each side before skin closure. Cephalothin sodium (40 mg/kg) was administered perioperatively, one dose preoperatively (intravenous), and three doses postoperatively (intramuscular).

Histologic Studies

After euthanizing the dog, a section of the frontal bone encompassing the implant sites was removed en bloc using an oscillating saw. The specimen was fixed in 10% buffered formaldehyde solution and processed to produce an undecalcified preparation. The undecalcified preparation served to preserve the hydroxyapatite implant for microscopic studies. The processing methods were as follows. The specimens were (1) rinsed in water and placed in a 70% alcohol solution; (2) processed under vacuum through sequential changes of 95% alcohol solutions (24 hours total) and two changes of 100% alcohol solutions (24 hours total) for dehydration; (3) embedded in methylmethacrylate; (4) sectioned to 80 to 100 μm and ground to a thickness of 40 μm; and (5) stained with Paragon stain (Ladd Multiple Stain, Burlington, Vt). This method of staining allowed good differentiation between fully mineralized bone and osteoid. The cellular and soft-tissue components stain deep blue, mineralized bone stains a flesh color, and osteoid stains magenta.

Gross examination of the specimens was performed with a dissecting microscope (Zeiss OMI-1, Carl Zeiss Inc, Thornwood, NJ) at ×2.5 magnification to evaluate the integrity and contour of the implant and its integration with the underlying bone. Microscopic examination was carried out with an Olympus BH-2 microscope (Olympus Corp, Lake Success, NY). Histometric analysis was performed with a microscope using a Wiebel grid at ×100 magnification. The proportion of bone and osteoid was compared with the amount of residual hydroxyapatite within the implant for the two dogs with the longest follow-up, group 3.

RESULTS

Each of the six dogs survived the planned duration of implantation. There were no toxic reactions or implant extrusions. One of the dogs in group 3 suffered a wound infection on the side of the cement and collagen membrane tubule implant 1 week postoperatively. The implant was removed, the wound was irrigated, and antibiotic therapy was instituted for 1 week. A new implant was inserted at the same site shortly after resolution of the infection. No

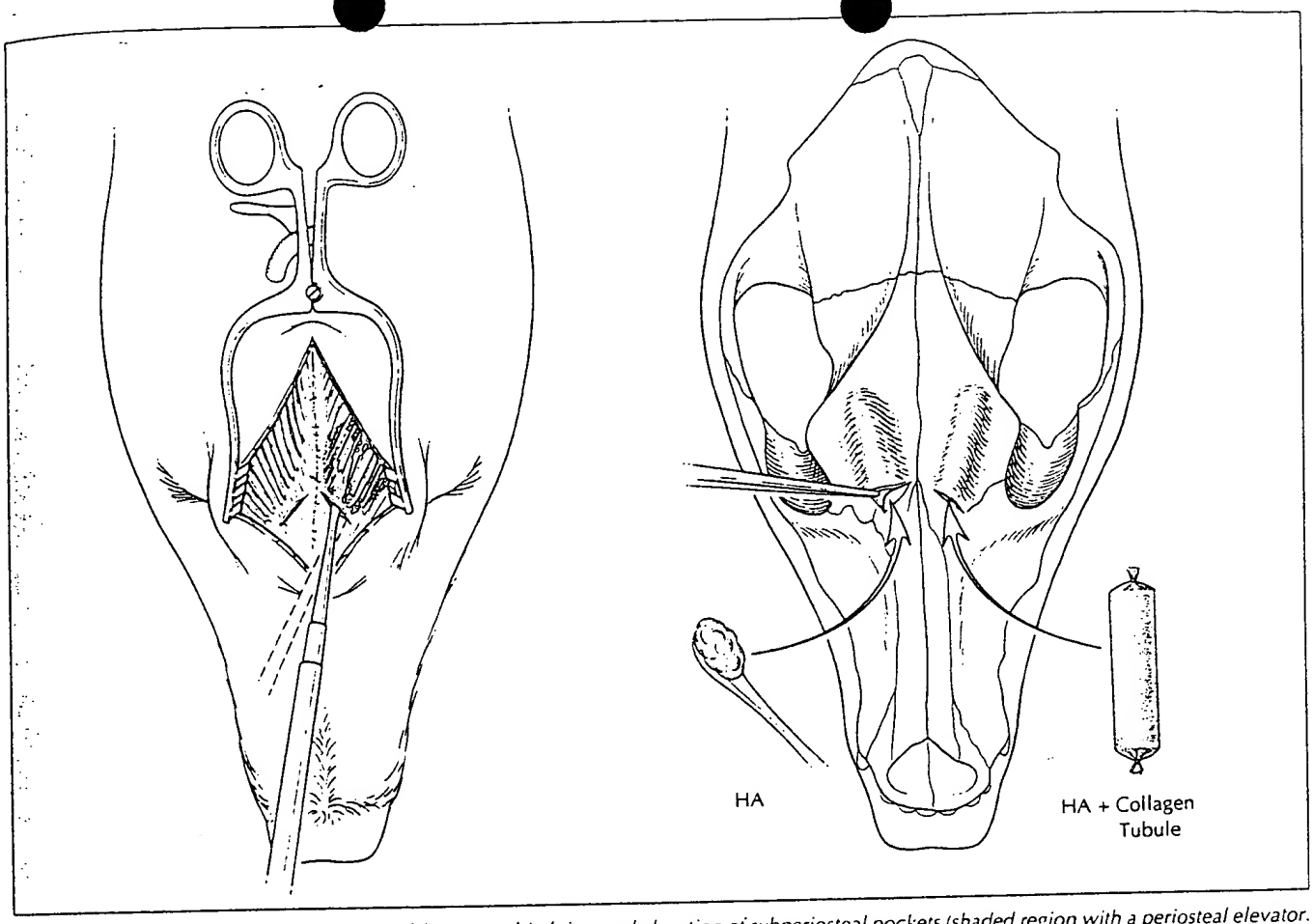

Fig 2.—*Operative technique. Left, Exposure of the supraorbital rims and elevation of subperiosteal pockets (shaded region with a periosteal elevator. Right, Insertion of the hydroxyapatite cement (HA) into the subperiosteal pockets: directly onto bone with a periosteal elevator on the right side and contained within a collagen membrane tubule on the left side.*

further complications developed in that dog. That dog was one of two to have had drains placed in the wound for 24 hours postoperatively. Manipulation of the drain by the dog resulted in self-removal of the drain and partial wound dehiscence. Subsequent to that, drains were not inserted postoperatively, and no additional complications developed.

Gross Examination

On gross inspection and palpation bimonthly, all six dogs maintained prominent ridges bilaterally at the site of the implants throughout the entire duration of the experiment. Gross inspection of autopsy specimens from all six dogs revealed that variable quantities of the hydroxyapatite implant had been replaced by bone that was inserted without collagen membrane. The quantity of implant replaced by bone was noted to be considerably greater at 6 months compared with 3 months, and even more at 9 months. On the left side, where the hydroxyapatite cement was implanted with collagen membrane, the quantity of hydroxyapatite cement in necropsy specimens was noted to be the same as immediately after implantation. In all six dogs, the height of the supraorbital ridge at the implant site on either side was within 1 mm of the height of the original implant. With all implants, the surface that was not in contact with bone was covered by a new fibrous capsule with neovascularization of the implant (Fig 3). On palpation, the implants were solidly integrated to the underlying bone bilaterally.

Microscopic Examination

On the side where the hydroxyapatite cement was implanted without collagen membrane, progressive replacement of the implant by bone was observed with time. At 3 months, new dense bone with a woven architecture was observed at the implant-bone interface. At 6 months, there was extension of the new bone into the implant. At 9 months, the new bone further extended into and divided the implant at one or more sites (Fig 4, top). Fully mineralized bone as well as an advancing front of osteoid extending into the implant were observed at the implant-bone junction (Fig 4, center). Histometric analysis of the two 9-month specimens revealed that the proportion of hydroxyapatite implant replaced by bone and osteoid was 42% and 45%. On the side where the hydroxyapatite cement was implanted by containment within collagen tubules, primarily a fibrous union was observed at the implant-bone interface for all three groups of dogs. The implant was not replaced by bone (Fig 4, top and bottom).

The inflammatory response to all of the implants was minimal. A few polymorphonuclear leukocytes and monocytes were observed in the soft tissue surrounding the implants at 3 months and were not seen in the 6- and 9-month specimens. There was no foreign body giant cell formation. A fibrous capsule surrounded the outer surface of the implants in all specimens. New blood vessels were seen growing into the implant through this fibrous capsule on the outer surface.

Fig 3.—*Gross appearance of the implant sites 9 months postoperatively, with hydroxyapatite on the right and hydroxyapatite-collagen on the left. A fibrous capsule with new blood vessels surrounds the outer surface of the implants.*

COMMENT

Hydroxyapatite has been used clinically as bone substitute in oromaxillofacial surgery and dentistry for more than 15 years. The major use has been for augmentation of the alveolar ridge to improve denture fitting in the edentulous patient.[21-23] To date, all clinically used hydroxyapatite preparations have been preformed hard ceramic materials, either ground into granules or shaped into blocks. The ceramic form of hydroxyapatite has significant limitations: (1) blocks cannot be accurately contoured, and they are fragile and (2) granules lack structural stability until ingrown by fibro-osseous tissue, a process that can take several months. The hydroxyapatite used in this study is not preformed. It is initially inserted as calcium phosphate cement, which can be contoured to the desired shape, and then sets in vivo at a physiologic pH and temperature to structurally stable hydroxyapatite. Under in vitro conditions at 37°C, the cement hardens in approximately 15 to 20 minutes.[27] In contrast to the preformed (ceramic) hydroxyapatite, which is not resorbed in significant quantities, the hydroxyapatite cement slowly resorbs with time and is replaced by bone in an approximate 1:1 ratio with minimal ingrowth of fibrous tissue, resulting in no functional loss of volume.[28-31]

In this study, when the hydroxyapatite cement was placed directly onto bone, approximately half of the implant was resorbed and then replaced with bone and osteoid by 9 months, resulting in no significant decrease in the height of the implant. The mechanism of bone replacement appears to be related to osteoconductive properties of nonceramic hydroxyapatite. When placed in contact with bone, it induces osteoid deposition at the interface. This front of the osteoid advances into the implant, with the implant serving as a scaffold through which bone can grow.[34] Our results are a significant improvement over the results that have been reported with ceramic hydroxyapatite implants. A study by Felsenfeld et al[35] indicated that only 17% of the pores within the porous ceramic hydroxyapatite blocks were filled by bone and 44% were filled by soft tissue over a 2-year period. The lack of bony union or osteoid replacement when the hydroxyapatite cement was implanted after containment within collagen tubules suggests that the hydroxyapatite cement must be in contact with bone at the time of implantation to initiate the process of osteoid deposition.

The soft-tissue cellular response to hydroxyapatite cement or hydroxyapatite-collagen implants used in this study was favorable. The lack of foreign body giant cell formation and absence of a significant inflammatory response is significantly less than the reactions that have been observed with other synthetic implants, such as Silastic, Proplast, or methylmethacrylate. Such an absence of foreign body reaction suggests that the extrusion rate of these hydroxyapatite implants should be less than that of other polymer implants. A solid bony union between the

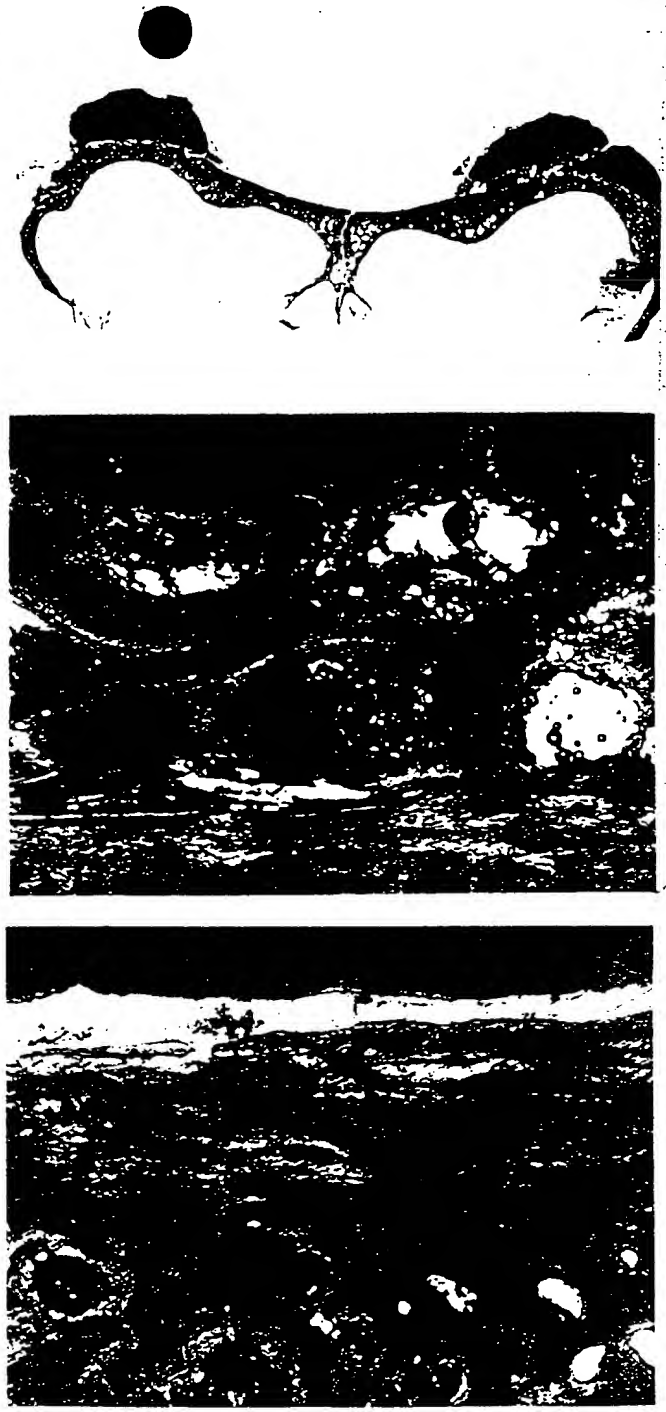

Fig 4.—*Histologic appearance 9 months postoperatively (Paragon stain). Mineralized bone stains a flesh color, osteoid stains magenta, and soft tissue stains deep purple. Top, Photomicrograph of an 80-μm-thick section of the implants (actual size), with hydroxyapatite on the right and hydroxyapatite-collagen on the left. Center, Junction of hydroxyapatite implant and bone showing fully mineralized bone as well as new dense bone extending into the implant (×10). Bottom, A fibrous union with no osteoid deposition at the junction of hydroxyapatite-collagen implant and bone (×10).*

hydroxyapatite cement and the underlying bone, with subsequent replacement by living bone, also should decrease the likelihood of implant extrusion. Despite the fact that the hydroxyapatite-collagen implant demonstrated only fibrous encapsulation rather than replacement with living bone, the implant was firmly attached to the underlying bone and stable by palpation. The lack of implant mobility should minimize the risk of extrusion and resorption, even if a bony union is not present. Unlike other alloplastic materials, fibrous encapsulation of the hydroxyapatite-collagen implant did not result from a sustained inflammatory response and did not show an increased risk of migration or extrusion. This is probably due to the fact that both hydroxyapatite and collagen are naturally occurring, biocompatible substances.

The use of experimental bone growth (morphogenic) proteins contained in various carrier matrices for osseous replacement was recently reported by Toriumi et al.[36] Though these materials are promising and will undoubtedly find application for selected problems in osseous replacement and fracture healing, none as yet can be delivered by a matrix that sets to a structurally stable implant. A significant advantage of hydroxyapatite cement over experimental bone growth proteins is that the cement can be modeled to a specific shape and sets within 15 minutes to a structurally stable implant. In contrast, bone growth proteins are delivered by matrices that resemble a thick paste or dense clot; they do not set and are not completely stable structurally for as long as 10 to 12 weeks. In addition, there is probably no advantage to growing bone for a non–stress-bearing application such as facial augmentation, as long as the proposed implant osseointegrates to the underlying bone and is well tolerated histologically. The hydroxyapatite cement demonstrates these two qualities, in addition to being replaced by bone over time without a change in implant shape. Long-term studies in large animals have proved that areas of the craniofacial skeleton reconstructed with the hydroxyapatite cement are stable with respect to their shape and volume regardless of the amount of replacement by bone (P.D.C., unpublished data, October 1, 1990). It is unknown whether bone produced by experimental bone growth proteins will maintain its augmented height over time, especially when that bone is not under stress. Studies with on-lay bone grafts suggest that progressive resorption with a change in augmented shape and height is the rule rather than the exception. In contrast, the cement and commercial ceramic forms of hydroxyapatite maintain their augmented height whether or not they are ingrown by bone.

This new hydroxyapatite cement potentially represents an ideal implant for facial skeletal augmentation, particularly in light of its osseous replacement with time, maintenance of implant height when placed directly onto bone, and setting properties, which allow it to set to a structurally stable implant. However, implantation of the cement in its free form is technique dependent. The implant must be placed in direct contact with bone, ie, subperiosteally, to promote ingrowth of bone with subsequent osteoid replacement of the implant. When implanted in free form, the opening of the subperiosteal pocket must be small to contain the cement within the pocket. In this study, a small periosteal elevator was used to place the cement into the pocket, which limited the ability to quantify precisely the amount of cement implanted. Therefore, it is more difficult to achieve a substantially augmented height when implanted in free form as compared with when it is contained within collagen tubules. A well-designed delivery system with a syringe and an appropriate size needle tip may allow easier and more accurate placement of the implant. Furthermore, the desired contour can be obtained by varying the size and shape of the collagen membrane. The disadvantage of containing the hydroxyapatite cement in collagen tubules is that the presence of the collagen membrane between the hydroxyapatite and underlying bone appears to interfere with osseointegration of the hydroxyapatite to the underlying bone and replacement of the implant by osteoid over time. On the other hand, the implant appears to remain extremely stable by palpation despite only a fibrous union to the underlying bone. Furthermore, unlike other synthetic implants that are in current use, the hydroxyapatite-collagen implant demonstrated no significant loss of volume over time. Such degree of stability as well as the lack of resorption supports the feasibility of implanting the hydroxyapatite cement by containment within bioabsorbable membranes.

The results of this study indicate that hydroxyapatite cement, either by itself or when contained within a bioabsorbable membrane, can be used successfully to augment the non–stress-bearing craniofacial skeleton. It has distinct advantages over existing implant materials in that the material is implanted in cement form and can therefore be easily contoured to the desired shape intraoperatively. Furthermore, the risk of implant extrusion is minimal, there is no significant loss of implant height over time, and the material is highly biocompatible. When in direct contact with viable bone, the implant is replaced by bone over time, resulting in no significant loss of reconstructed volume. Potential clinical applications would include those situations where aesthetic or reconstructive augmentation of the non–stress-bearing craniofacial skeleton is desired.

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